VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the specification:

Please replace the first paragraph, lines 1-10, on page 7 with the following amended paragraph:

A contaminant analysis of hyaluronidase purified from *S. hyalurolyticus* (Amano Enzyme Company, Nagoya, Japan) demonstrates significantly reduced protease activities in the range of 0.00316 units per mL to 0.0188 units per mL and substantially higher hyaluronidase activities (152 to 218 TRU per mL) than found in the bovine enzyme. The *S. hyalurolyticus* hyaluronidase activity is at least about 10 TRU per mL; whereas, the bovine enzyme hyaluronidase activities range from 2.44 to 4.82 TRU per mL. Preferably, the *S. hyalurolyticus* hyaluronidase activity is in the range of about 100-300 TRU per mL, as noted in the example above (152 to 218 TRU per mL). This means that less *S. hyalurolyticus* enzyme is necessary per treatment. Although the hyaluronidase obtained from *S. hyalurolyticus* is reported to be susceptible to protease inactivation, less contaminating protease means that the enzyme is more stable for ophthalmic use. These advantages of easier and higher yield purification, higher enzyme activity and use in a system that is essentially free from inactivating proteases, make this source of hyaluronidase a better candidate for ophthalmologic uses.

In the claims:

Please replace the pending claims 1-3 with the following amended claims 1-3:

1. (Amended) A method for accelerating the clearance of hemorrhagic blood from the vitreous humor of a mammalian eye, comprising the step of[;] injecting into the

vitreous humor a solution which contains hyaluronidase from *Streptomyces hyalurolyticus* to provide a dose having a hyaluronidase activity of at least about 10 Turbidity Reducing Units (TRU) of said hyaluronidase, said solution being[:] [i] essentially free of contaminating protease.

2. (Amended) A method of treating eye disorders comprising the step of applying essentially protease-free hyaluronidase from *Streptomyces hyalurolyticus* to the eye, wherein said hyaluronidase is dissolved in a saline solution.

3. (Amended) The method of claim 2, wherein treating of [an] said eye disorders is the clearing of hemorrhagic blood from the vitreous humor of a mammalian eye by using essentially protease-free hyaluronidase from *Streptomyces hyalurolyticus* the amount of the hyaluronidase being sufficient to clear the blood.

Please add the following new claim:

9. (New) The method of claim 1, wherein said hyaluronidase activity is in the range of about 100-300 Turbidity Reducing Units (TRU) of said hyaluronidase.

REMARKS

In the Office Action the Examiner objected to Claim 3 and rejected all pending claims 1-8 under 35 USC 112, 102, and 103. Applicant respectfully traverses these rejections.

Objection to Claim 3

The Examiner objected to Claim 3 due to the informality of semantically incorrect phraseology. Applicant has amended Claim 3 above to overcome this objection. Accordingly, Applicant respectfully requests that the objection be withdrawn.

Rejection Under 35 USC 112

The Examiner rejected Claim 1 under 35 USC 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors, at the time the application was filed, had possession of the claimed invention and because the specification does not reasonably provide enablement.

Specifically, the Examiner asserts that while claim 1 recites 10 TRU, the specification recites only 152-218 TRU. The page 7, paragraph 1 of the specification has been amended to clarify while about 100-300 TRU (152-218 TRU) is the preferred range of hyaluronidase activity, at least about 10 TRU is a possible hyaluronidase activity level. Since both 10 TRU and 152-218 TRU was originally disclosed in the original application as filed, the amendment does not comprise new matter. Claim 1 has been amended and Claim 9 has been added in order to more clearly claim the invention.

Applicant believes that the above amendments to the claims and specification overcome this rejection. Accordingly, Applicant respectfully requests that this rejection be withdrawn.

Rejection Under 35 USC 102

The Examiner rejected Claim 2 under 35 USC 102(b) as being anticipated by Schwartz et al. The Examiner asserts that Schwartz discloses a method of intraocularly injecting a mixture of chrondroitin sulfate, hyaluronic acid, and hyaluronidase derived from Streptomyces. Applicant asserts that this mixture does not anticipate Applicant's invention as now claimed.

Scwartz discloses a mixture of hyaluronidase with a viscoelastic. In column 5, lines 50-57 of the Schwartz patent, Schwartz specifically requires that the degradative agent (e.g. hyaluronidase from Streptomyces) be mixed with a viscoelastic in order to prevent accumulation of local pockets of high concentrations of the degradative agent that could have potentially toxic effects. Further, when discussing the specific use of hyaluronidase from Streptomyces at column 7, lines 54-65, Schwartz requires dissolving the hyaluronidase with a solution other than a balanced saline, specifically the viscoelastic chondroitin sulfate, then mixing the hyaluronidase-chondroitin solution with Viscoat, the viscoelastic, which the hyaluronidase will degrade. In the disclosure, Schwartz makes clear the belief that introducing hyaluronidase from Streptomyces alone or dissolved in a saline solution into the eye will have a toxic effect on the eye, and, therefore, requires mixing the hyaluronidase with a viscoelastic.

Conversely, the present invention discloses injecting the hyaluronidase derived from Streptomyces hyalurolyticus dissolved in a balanced saline solution into the eye to treat eye disorders. Claim 2 has been amended to more clearly claim this solution. As Schwartz does not disclose injecting the only hyaluronidase derived from Streptomyces hyalurolyticus dissolved in a balanced saline solution into the eye, Schwartz clearly does not anticipate the present invention. Accordingly, Applicant respectfully requests that the 35 USC 102(b) rejection of claim 2 be withdrawn.

Rejection Under 35 USC 103

The Examiner rejected claims 1-3, 7 and 8 under 35 USC 103(a) as being unpatentable over Karageozian et al. in view of Schwartz et al., and further in view of Kaneko et al. The Examiner asserts that Karageozian discloses the use of hyaluronidase to accelerate the clearance of hemorrhagic blood from the vitreous humor and Kaneko discloses utilization of Streptomyces hyalurolyticus as a source of hyaluronidase.

As cited in the specification of the present invention, Applicant acknowledges Karageozian's disclosure of using bovine hyaluronidase to accelerate clearance of hemorrhagic blood from the vitreous humor and Kaneko's disclosure of deriving hyaluronidase from Streptomyces hyalurolyticus. Applicant, however, asserts that the combination of Karageozian, Schwartz, and Kaneko does not render the present invention obvious.

Karageozian discloses only using hyaluronidase derived from bovine testicles to accelerate the clearance of hemorrhagic blood, and further provides no motivation or suggestion for combining the invention of Karageozian with the invention of Kaneko. In

fact, Karageozian actually teaches away from Kaneko and the present invention in that Karageozian specifically states that using hyaluronidase derived from bovine testicles is preferred because of its lower toxicity than hyaluronidase derived from other sources. Additionally, as discussed above, Schwartz also stressed the danger of toxicity if hyaluronidase is injected into the eye alone without mixing with a viscoelastic, and only disclosed mixing hyaluronidase with at least one viscoelastic as a degrading agent for viscoelastic. Accordingly, Applicant asserts that there is no motivation to combine Karageozian and/or Schwartz with Kaneko.

Further, Applicant notes that as set forth in the present application, hyaluronidase derived from Streptomyces hyalurolyticus was considered inapplicable to the medical field due to its susceptibility to proteolytic inactivation. The present invention sets forth however, that the high enzyme level in hyaluronidase derived from Streptomyces hyalurolyticus outweighs any protease inactivation. Due to this high level of hyalurnoidase activity, less hyaluronidase derived from Streptomyces hyalurolyticus is required for any given procedure.

Given the above facts, namely that hyaluronidase derived from Streptomyces hyalurolyticus was considered to be unusable in the medical field and to have toxic effects in the eye, Applicant believes that the present invention was not obvious in view of Karageozian, Schwartz, and Kaneko. Karageozian, Schwartz, and Kaneko, neither individually nor in combination, disclose or suggest all aspects of the present invention. Accordingly, Applicant respectfully requests that the rejection be withdrawn.

The Examiner rejected Claims 2 and 4 under 35 USC 103(a) as being unpatentable over Harris et al. in view of Schwartz, and further in view of Kaneko. The

Examiner asserts that Harris et al. discloses the use of hyaluronidase in an amount sufficient to cause corneal softening; Schwartz et al. discloses injecting a mixture of chrondroitin sulfate, hyaluronic acid and hyaluronidase derived from Streptomyces; and Kaneko discloses utilization of Streptomyces hyalurolyticus as a source of hyaluronidase.

As cited in the specification of the present invention, Applicant acknowledges Harris's disclosure of using bovine hyaluronidase to soften the cornea of the eye in a form of orthokeratology or vision correction and Kaneko's disclosure of deriving hyaluronidase from Streptomyces hyalurolyticus. Applicant, however, asserts that the combination of Harris, Schwartz, and Kaneko does not render the present invention obvious.

Harris discloses only using hyaluronidase derived from bovine testicles to soften the cornea, and further provides no motivation or suggestion for combining the invention of Harris with the invention of Kaneko. Harris teaches using hyaluronidase from bovine testicles to soften the cornea. Specifically, Harris teaches using Wydase in the procedure, which directly teaches away from the present invention. Wydase is expensive and laborious to manufacture and is in short supply. The present invention provides a form of hyaluronidase derived from Streptomyces hyalurolyticus that is easy to manufacture, more potent than Wydase, and formerly believed inapplicable to the medical field. Additionally, as discussed above, Schwartz stressed the danger of toxicity if hyaluronidase is injected into the eye alone without mixing with a viscoelastic, and only disclosed mixing hyaluronidase with at least one viscoelastic as a degrading agent for viscoelastic. Accordingly, Applicant asserts that there is no motivation to combine Harris and/or Schwartz with Kaneko.

Further, as noted above, hyaluronidase derived from Streptomyces hyalurolyticus was considered inapplicable to the medical field due to its susceptibility to proteolytic inactivation. The present invention sets forth however, that the high enzyme activity level in hyaluronidase derived from Streptomyces hyalurolyticus outweighs any protease inactivation. Due to this high level of hyalurnoidase activity, less hyaluronidase derived from Streptomyces hyalurolyticus is required for any given procedure.

Given the above facts, Applicant believes that the present invention was not obvious in view of Harris, Schwartz, and Kaneko. Harris, Schwartz, and Kaneko, neither individually nor in combination, disclose or suggest all aspects of the present invention. Accordingly, Applicant respectfully requests that the rejection be withdrawn.

The Examiner rejected Claim 5 under 35 USC 103(a) as being unpatentable over Straus in view of Schwartz and further in view of Kaneko. The Examiner asserts that Straus discloses intraocularly injection a local anesthetic mixture including hyaluronidase; Schwartz et al. discloses injecting a mixture of chrondroitin sulfate, hyaluronic acid and hyaluronidase derived from Streptomyces; and Kaneko discloses utilization of Streptomyces hyalurolyticus as a source of hyaluronidase.

Applicant asserts that the combination of Straus, Schwartz, and Kaneko does not render the present invention obvious. As noted by the Examiner, Straus does not disclose using hyaluronidase derived from Streptomyces hyalurolyticus and does not suggest such use. Further, as previously stated above, Schwartz merely disclosed using a combination of hyaluronidase from Streptomyces and a viscoelastic to degrade viscoelastic while stressing the dangers of toxicity if hyaluronidase is injected into the eye alone without mixing with a viscoelastic. Schwartz does not suggest using hyaluronidase derived from

Streptomyces hyalurolyticus dissolved only in a saline solution to treat eye disorders. As also previously noted, the hyaluronidase derived from Streptomyces hyalurolyticus disclosed in Kaneko was widely believed inapplicable to the medical field. Accordingly, Applicant asserts that there is no motivation to combine Straus and/or Schwartz with Kaneko.

Given the above facts, Applicant believes that the present invention was not obvious in view of Straus, Schwartz, and Kaneko. Straus, Schwartz, and Kaneko, neither individually nor in combination, disclose or suggest all aspects of the present invention. Accordingly, Applicant respectfully requests that the rejection be withdrawn.

Finally, the Examiner rejected Claim 6 under 35 USC 103(a) as being unpatentable over Fedorov et al. in view of Scwartz and further in view of Kaneko. The Examiner asserts that Fedorov discloses a method of using hyaluronidase for preparing artificial lenses; Schwartz et al. discloses injecting a mixture of chrondroitin sulfate, hyaluronic acid and hyaluronidase derived from Streptomyces; and Kaneko discloses utilization of Streptomyces hyalurolyticus as a source of hyaluronidase.

Applicant asserts that the combination of Federov, Schwartz, and Kaneko does not render the present invention obvious. As noted by the Examiner, Federov does not disclose using hyaluronidase derived from Streptomyces hyalurolyticus and does not suggest such use. Further, as previously stated above, Schwartz merely disclosed using a combination of hyaluronidase from Streptomyces and a viscoelastic to degrade viscoelastic while stressing the dangers of toxicity if hyaluronidase is injected into the eye alone without mixing with a viscoelastic. Schwartz does not suggest using hyaluronidase derived from Streptomyces hyalurolyticus dissolved only in a saline

solution to treat eye disorders such as artificial lenses. As also previously noted, the hyaluronidase derived from Streptomyces hyalurolyticus disclosed in Kaneko was widely believed inapplicable to the medical field. Accordingly, Applicant asserts that there is no motivation to combine Federov and/or Schwartz with Kaneko.

Given the above facts, Applicant believes that the present invention was not obvious in view of Federov, Schwartz, and Kaneko. Federov, Schwartz, and Kaneko, neither individually nor in combination, disclose or suggest all aspects of the present invention. Accordingly, Applicant respectfully requests that the rejection be withdrawn.

CONCLUSION

In light of the above amendments and arguments, Applicant respectfully asserts that the present application is now in condition for allowance. Accordingly, Applicant requests that all objections and rejections set forth in the Office Action be withdrawn.

Respectfully submitted,

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By: Kimberly D. Snead
Kimberly D. Snead
Reg. No. 45,119

Parker & DeStefano
300 Preston Avenue
Suite 300
Charlottesville, VA 22902
Telephone: 434-817-6606
Facsimile: 434-817-6610